PCT/IB04/00821 348

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.**354/Del/03** dated **21st March 2003.***

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Witness my hand this 13th day of April 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

0354-03

Govt. of India Patent Office New Delhi Received Rs. 5000/- in cash. Cheque/M.O./I.P.O./D.D. on 21 MAR 2003 Vide Entry No. 1153 in the Register of Valuables A.O. Cashier

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A61K31/00

21 MAR 2003

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 , Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF WATER-SOLUBLE TABLETS OF METFORMIN"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. DEEPAK MURPANI
b. ROBERT KENNEDY
c. SANJEEV SETHI
d. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

ORIGINAL

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), India.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10
Fax No. (91-124) 2342027

6. Following declaration was given by the inventors in the convention country:

We, DEEPAK MURPANI, ROBERT KENNEDY, SANJEEV SETHI, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(DEEPAK MURPANI)

b.

(ROBERT KENNEDY)

c.

(SANJEEV SETHI)

d.

(RAJEEV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **688515** dated :**11.03.2003** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **21ST** day of **March, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

A PROCESS FOR THE PREPARATION OF WATER-SOLUBLE TABLETS OF METFORMIN

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of water-soluble tablet comprising a pharmaceutically acceptable salt of metformin, which dissolves to form a clear aqueous solution.

Diabetes Mellitus is one of the most common disease affecting humans, which is characterized by an inappropriate elevation of blood glucose levels. The primary goal in the treatment of diabetes is to maintain blood glucose levels as close to normal as possible. Type I Diabetes Mellitus is due to absence of insulin in the individual and medication requires subcutaneous injections of insulin. Type II Diabetes Mellitus is due to decreased circulating insulin. For Type II diabetics, the oral hypoglycemic therapy or in some cases insulin therapy is required to control glucose levels and thus minimize complications related to the disease.

In oral hypoglycemic therapy, one of the compounds commonly used to treat diabetes is metformin a biguanide derivative. U. S. Patent No. 3,174,921 discloses various pharmaceutically acceptable salts of metformin, for example, phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate and glycolate. U. S. Patent No. 6,031,004 discloses metformin salts of dibasic acids, such as fumarate and succinate.

It has generally been observed that patient compliance is drastically reduced due to the inconvenience caused in swallowing tablets. The large sized tablets are not preferred by elderly or children due to difficulty in swallowing and in many cases; the patient's ability to swallow anything is compromised. Moreover, when a drug, such as metformin, has an unpleasant bitter taste further reduces patient compliance. Therefore, it would be desirable to develop an oral dosage form, such as a water-soluble tablet, of metformin, which is easy to consume and has a pleasant palatability.

We have surprisingly discovered that metformin water-soluble tablets having pleasant taste and capable of dissolving within 3 minutes in water without residual particulate matter can be easily prepared by use of water soluble sugar alcohols and other water-soluble excipient(s). The sugar alcohols such as sorbitol, mannitol, xylitol, isomalt and hydrogenated starch hydrolysates not only help in quick

disintegration of the tablet but also provide compressible properties to the bulk. Therefore metformin water-soluble tablets can be prepared by compressing a mixture of a pharmaceutically acceptable salt of metformin, water-soluble sugar alcohols and other water-soluble excipient(s).

The process provides water-soluble tablets comprising a pharmaceutically acceptable salt of metformin, which are rapidly soluble in aqueous media and provide an easy mode of administration. These tablets may also be swallowed as other conventional tablets.

The tablet has sufficient hardness and friability to withstand impacts during manufacturing, packaging and transport.

Therefore in one general aspect it provides a water-soluble tablet comprising a pharmaceutically acceptable salt of metformin capable of dissolving within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to give a clear solution.

In another general aspect it provides a water-soluble tablet comprising a pharmaceutically acceptable salt of metformin having hardness of about 2 kP to about 8 kP and capable of dissolving within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear solution.

In another general aspect it provides a water-soluble tablet comprising a pharmaceutically acceptable salt of metformin having pleasant taste.

In another general aspect it provides a water-soluble tablet capable of dissolving within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution, comprising a pharmaceutically acceptable salt of metformin, water-soluble sugar alcohol(s) and other water-soluble excipient(s).

In another general aspect it provides a water-soluble tablet capable of dissolving within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution, comprising a pharmaceutically acceptable salt of metformin, xylitol, mannitol and other water-soluble excipient(s).

In another general aspect it provides a process for the preparation of a water-soluble tablet comprising a pharmaceutically acceptable salt of metformin having hardness of about 2 kP to about 8 kP and capable of dissolving within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear solution.

In another general aspect it provides a process for the preparation of a water-soluble tablet comprising a pharmaceutically acceptable salt of metformin having pleasant taste.

In another general aspect it provides a process for the preparation of a water-soluble tablet which comprises direct compression of a blend of a pharmaceutically acceptable salt of metformin with water-soluble sugar alcohols and other water-soluble excipient(s); and dissolves within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution.

In another general aspect it provides a process for the preparation of water-soluble tablet which comprises direct compression of a blend of a pharmaceutically acceptable salt of metformin with xylitol, spray dried mannitol and other water-soluble excipient(s); and dissolves within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution.

In another general aspect it provides a process for the preparation of water-soluble tablet which comprises wet granulating a mixture comprising a pharmaceutically acceptable salt of metformin, binder, water-soluble sugar alcohols and other water-

soluble excipient(s); and dissolves within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution.

In another general aspect it provides a process for the preparation of water-soluble tablet which comprises wet granulating a mixture comprising a pharmaceutically acceptable salt of metformin, binder, xylitol, spray dried mannitol and other water-soluble excipient(s); and dissolves within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution.

In another general aspect it provides a process for the preparation of water-soluble tablet which comprises dry granulation by slugging or compaction of a mixture comprising a pharmaceutically acceptable salt of metformin, binder, water-soluble sugar alcohols and other water-soluble excipient(s); and dissolves within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution.

In another general aspect it provides a process for the preparation of water-soluble tablet which comprises dry granulation by slugging or compaction of a mixture comprising a pharmaceutically acceptable salt of metformin, binder, xylitol, spray dried mannitol and water-soluble excipient(s); and dissolves within 3 minutes, in particular in about 2 minutes and more particularly in about 1 minute in about 30 ml, in particular about 20 ml and more particularly in about 15 ml water to form a clear aqueous solution.

The "water-soluble tablet" herein means as described in British Pharmacopoeia 1988, Vol II, an uncoated tablets that dissolve in water and the solution produced may be slightly opalescent due to added substances used in the manufacture of the tablets.

The term "clear aqueous solution" herein means the solution formed after the tablet has completely dissolved should appear transparent to the naked eye. However, the

solution produced may be opalescent due to some water-insoluble impurities present in added excipients.

The pharmaceutically acceptable salt of metformin include phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate, glycolate, salts of dibasic acids, such as fumarate and succinate. Particularly suitable salt of metformin is hydrochloride salt. The pharmaceutically acceptable salt comprises not more than 95% weight by weight of the tablet.

The water-soluble sugar alcohols for example may be selected from sorbitol, mannitol, spray dried mannitol, xylitol, erythritol isomalt and hydrogenated starch hydrolysates and combinations thereof. Particularly suitable are xylitol and spray dried mannitol. Mannitol can be spray-dried mannitol, which is available under the trade name Pearlitol. It is a free flowing directly compressible sugar and has cooling taste due to negative heat of solution. It gives tablets of good hardness and also facilitates quick dissolution. The sugar alcohol may comprise from about 10% to about 95% weight by weight of the tablet. In particular it may comprise from about 30% to about 70% weight by weight of the tablet.

Besides a pharmaceutically acceptable salt of metformin and water-soluble sugar alcohols, the tablet may comprise of water-soluble binders, lubricants, sweeteners and flavouring agents.

The binder may be selected from soluble starch, polyvinylpyrrolidone, cellulose ethers, gums, carboxyvinyl polymer(s) or combinations thereof.

The lubricant may be selected from polyethylene glycol, sodium propionate, sucrose, sodium chloride, silicon oil, simethicone, polyvinylpyrrolidone, DL-leucine, sodium benzoate, boric acid sodium lauryl sulphate, magnesium lauryl sulphate and combinations thereof. Particularly suitable is polyethylene glycol. Still more particularly suitable is pulverized or micronised polyethylene glycol having a particle size of about 90% less than 250μ. Polyethylene glycol may be selected from different molecular weight polyethylene glycols, such as those having molecular weights from

about 1500 to about 20,000. Particularly suitable Polyethylene glycols are those having molecular weights from about 3500 to about 8000. The polyethylene glycol may comprise from about 0.1% to about 10% weight by weight of the tablet, particularly from about 2% to about 10% weight by weight of the tablet.

The sweetener may be selected from aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.

The flavouring agents may be selected from strawberry aroma, raspberry aroma, cherry flavour, lime flavour, fruit extracts, citrates and tartarates.

The tablet can be prepared by any conventional tableting method. In direct compression method, a pharmaceutically acceptable salt of metformin and sugar alcohol(s) and other water-soluble excipients may be sifted through a mesh of suitable size. The sifted blend may be mixed with lubricant and compressed using suitable tooling.

In wet granulation method, a pharmaceutically acceptable salt of metformin may be mixed with a binder and granulated with purified water. Alternatively, a pharmaceutically acceptable salt of metformin may be mixed with sugar alcohol(s) and granulated with a binder solution. The granules can be dried and mixed with other excipient(s) and compressed using suitable tooling.

In dry granulation the blend of all the ingredients can be compacted to make granules of suitable size and mixed with lubricant and compressed.

Tablet in particular is the final dosage form, however granules comprising a pharmaceutically acceptable salt of metformin and water-soluble sugar alcohols and other water-soluble excipients can also be prepared and packed into sachets, bottles or other suitable packaging devices meant for unit/multiple dosage. These granules can be dissolved in water to give a clear solution and consumed.

The following examples are given for purpose of illustrating the present invention and not intended to limit the scope in any way.

Example 1

The tablets of example 1 were formulated with metformin hydrochloride (500mg); spray-dried mannitol (200mg), xylitol (200mg); aspartame (45mg); monosodium citrate (20mg); and micronised polyethylene glycol (25mg). Metformin, spray-dried mannitol, xylitol, aspartame and monosodium citrate (20mg) were sifted through a suitable mesh. The micronised polyethylene glycol was mixed with the above sifted blend and compressed into a tablet using appropriate tooling. The tablets thus obtained when dropped in 15 ml of water, dissolved quickly to give a clear solution.

Example 2

The tablets of example 2 were formulated with metformin hydrochloride (500mg); polyvinyl pyrrolidone, (10mg); spray-dried mannitol (200mg), xylitol (200mg); aspartame (45mg); monosodium citrate (20mg); and micronised polyethylene glycol (25 mg). The pharmaceutically acceptable salt of metformin and polyvinyl pyrrolidone were mixed in a blender and granulated with purified water. The granules were dried and mixed with spray-dried mannitol, xylitol, aspartame and monosodium citrate. The above blend was then mixed with micronised polyethylene glycol and compressed using appropriate tooling. The tablets thus obtained when dropped in 15 ml of water, dissolved quickly to give a clear solution.

The compositions of example 1-2, prepared using metformin hydrochloride are listed in Table 1.

Table 1

Composition	Example 1	Example 2
Metformin hydrochloride	500mg	500mg
Polyvinylpyrrolidone		10mg
Xylitol	200mg	200mg
Mannitol (spray-dried)	200mg	200mg
Aspartame	45mg	45mg
Monosodium citrate	20mg	20mg
Micronised polyethylene glycol	25mg	25mg
Purified water		q.s.
Total weight		

WE CLAIM:

1. A process for the preparation of a water-soluble tablet wherein the process comprises compressing a mixture of:
   (a) a pharmaceutically acceptable salt of metformin
   (b) water-soluble sugar alcohol(s);
   (c) other water-soluble excipients
   which tablet dissolves in about 3 minutes in about 30 ml of water to give a clear solution.
2. The process according to claim 1 wherein the tablet dissolves in water within two minutes to give a clear solution.
3. The process according to claim 1 wherein the tablet dissolves in water within one minute to give a clear solution.
4. The process according to claim 1 wherein the tablet is dissolved in about 20 ml of water.
5. The process according to claim 1 wherein the tablet is dissolved in about 15 ml of water.
6. The process according to claim 1 wherein the mixture is formulated into a tablet by direct compression.
7. The process according to claim 1 wherein the mixture is granulated prior to compression.
8. The process according to claim 7 wherein the mixture is wet granulated.
9. The process according to claim 7 wherein the mixture is dry granulated.
10. The process according to claim 1 wherein the pharmaceutically acceptable salt of metformin is phosphate, sulfate, hydrochloride, salicylate, maleate, benzoate, ethanedisulfonate, fumarate, glycolate, salts of dibasic acids such as fumarate and succinate.
11. The process according to claim 10 wherein the pharmaceutically acceptable salt is hydrochloride.
12. The process according to claim 1 wherein a pharmaceutically acceptable salt of metformin comprises not more than 95% weight by weight of the tablet.
13. The process according to claim 1 wherein the sugar alcohol(s) is selected from sorbitol, mannitol, spray-dried mannitol, xylitol, erythritol, isomalt and hydrogenated starch hydrolysates and combinations thereof.

14. The process according to claim 13 wherein the sugar alcohol(s) is xylitol.
15. The process according to claim 13 wherein the sugar alcohol(s) is mannitol.
16. The process according to claim 13 wherein the sugar alcohol(s) is a mixture of xylitol and mannitol.
17. The process according to claim 1 wherein the other water-soluble excipients include binders, lubricants, sweeteners, and flavouring agents.
18. The process according to claim 17 wherein the binder is selected from soluble starch, polyvinylpyrrolidone, cellulose ethers, gums and carboxyvinyl polymer(s).
19. The process according to claim 18 wherein the binder is polyvinylpyrrolidone.
20. The process according to claim 17 wherein the lubricant is selected from polyethylene glycol, sodium propionate, sucrose, sodium chloride, silicon oil, simethicone, polyvinylpyrrolidone, DL-leucine, sodium benzoate, boric acid, sodium lauryl sulphate, magnesium lauryl sulphate.
21. The process according to claim 20 wherein the lubricant is polyethylene glycol.
22. The process according to claim 21 wherein the polyethylene glycol pulverized/micronised.
23. The process according to claim 22 wherein the polyethylene glycol has particle size of from about 90% less than 250μ.
24. The process according to claim 21 wherein the polyethylene glycol has molecular weight of form about 3500 to about 20,000.
25. The process according to claim 24 wherein the polyethylene glycol has molecular weight of from about 3500 to about 8000.
26. The process according to claim 25 wherein the polyethylene glycol has molecular weight of 6000.
27. The process according to claim 25 wherein the polyethylene glycol has molecular weight of 8000.
28. The process according to claim 20 wherein the lubricant is sodium propionate.
29. The process according to claim 17 wherein the sweetener is selected from aspartame, saccharine sodium, glycine, lactose, dextrose, fructose, maltose, sorbitol and sucrose.
30. The process according to claim 29 wherein the sweetener is aspartame.

31. The process according to claim 1 wherein the tablet comprises a pharmaceutically acceptable salt of metformin, xylitol, spray-dried mannitol and micronised polyethylene glycol and which tablet dissolves in about 15ml of water within about 1 minute to give a clear solution.

32. A process for the preparation of a water-soluble tablet which comprises direct compression or wet granulation or dry granulation prior to compression, of a blend of a pharmaceutically acceptable salt of metformin, sugar alcohol(s) and micronised polyethylene glycol substantially as described and illustrated by the examples herein.

Dated this **21ST** day of **March, 2003.**

For RANBAXY LABORATORIES LIMITED

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to a process for the preparation of water-soluble tablet comprising a pharmaceutically acceptable salt of metformin, which dissolves to form a clear aqueous solution. The process provides water-soluble tablets comprising a pharmaceutically acceptable salt of metformin, which are rapidly soluble in aqueous media and provide an easy mode of administration.